

Midodrine Exacerbates Promethazine-induced Akathisia

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**To the editor:**

The study of physiological changes during spaceflight, and the pursuit of remedies to counteract those changes, often requires unique research protocols that lead to unexpected findings; some with important clinical implications. In our research into the development of treatments to counteract the detrimental cardiovascular effects of spaceflight, we have discovered an important drug interaction between promethazine and midodrine.

Promethazine has been the antiemetic of choice by NASA flight surgeons for about 15 years for the treatment of postflight nausea and vomiting . This laboratory has long pursued a pharmacological countermeasure for postflight orthostatic hypotension. We chose to evaluate midodrine because it is fast-acting, and has no cardiac or central side effects (4). Because midodrine and promethazine would likely be used together on landing day, we designed a study to determine if promethazine would counteract the positive effects of midodrine on orthostatic tolerance.

**Methods**

Ten healthy subjects gave written, informed consent to participate in this protocol, which was approved by the Johnson Space Center Committee for the Protection of Human Subjects; one subject withdrew from the study. The remaining subjects received all of four treatments, in random order (numbers 1-4 drawn from hat), separated by at least four days, with all combinations of 10 mg oral midodrine, 25 mg intravenous promethazine (infused over 12 minutes) and appropriate placebos (identical in appearance to test drugs). No subject had received any other medication within 24 hours prior to any testing. We discovered a profound akathisia when

midodrine and promethazine were given together and quantified severity with the Barnes global akathisia score. (2). Data were normally distributed, and had equal variance. Treatments were compared using repeated measures ANOVA with a Bonferroni ad hoc test..SigmaStat<sup>®</sup> software was used. Significance was set at  $p \leq 0.05$ . The tilt tolerance data will be reported separately.

## Results

Akathisia was experienced by: no subject with placebo alone; no subject with midodrine alone: four subjects with promethazine alone; and 6 subjects with midodrine and promethazine together. In addition, the severity of akathisia, measured by the Barnes global akathisia rating, was significantly greater ( $p=0.047$ ) with midodrine and promethazine together ( $2.0 \pm 0.6$  SEM) than with promethazine alone ( $0.8 \pm 0.4$  SEM).

## Comments

The fact that promethazine and midodrine together produced such profound akathisia in a majority of our subjects was unexpected. While, it is well known that phenothiazines (including promethazine) tend to induce akathisia (3), there have been no report that midodrine induces akathisia. However, both drugs are metabolized by the cytochrome P450 isozyme CYP2D6 (1, 6). One could expect that promethazine, given in the presence of midodrine, would have increased bioavailability and decreased clearance. The highly polymorphic nature of this enzyme in the population would also suggest that poorer metabolizers would be more susceptible to this kinetic interaction (6). Since its approval by the FDA, midodrine has become a first line

treatment for patients with orthostatic hypotension due to various autonomic neuropathies (5). Physicians who encounter these patients, particularly in acute settings, should be aware of this drug interaction and take careful histories regarding midodrine therapy before prescribing promethazine, or any other drug metabolized by CYP2D6. NASA has already taken the step of prohibiting the use of these two drugs together.

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This work was entirely supported by NASA grant NAS9-97005 to Dr. Meck, a NASA civil servant. She was responsible for all aspects of the study and preparation of the manuscript. Dr. Meck had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analysis was performed by Dr. Platts.

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